I. AMENDMENT

Please amend claims 27 and 39 to read as follows.

27. (Amended) The method of claim 1, wherein the thiazolidinedione compound is contacted with the cancer cell at the same time as contact with the chemotherapeutic drug.

39. (Amended) The method of claim 27, wherein the thiazolidinedione and the chemotherapeutic drug are combined in a therapeutic formulation.

II. RESPONSE TO OFFICE ACTION

A. Status of the Claims and Specification

Claims 1-46 were rejected by the Office Action dated April 23, 2003. Claim 27 and 39 stand rejected under 35 U.S.C. § 112, second paragraph. Claims 1-8, 16-23, 28, 30, 33-35 and 40-41 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Urban *et al.* (U.S. Patent No. 5,814,647). Claims 1, 16-25, 28, 29 and 36-38 are rejected under 35 U.S.C. 103(a) as being obvious over Urban *et al.* (U.S. Patent 5,814,647) in view of Medenica *et al.* (U.S. Patent 5,736,129). Claims 1, 25 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Urban *et al.* in view of Medenica *et al.* and further in view of Jin *et al.* (U.S. Patent 6,251,871). Claims 1, 28 and 30-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Urban *et al.* in view of Roth *et al.* (U.S. Patent 5,747,469). Claims 1, 9, 11-14, 40 and 43-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Urban *et al.* in view of Pitot. Applicants' response thereto is set out in detail below.

Claims 27 and 39 have been amended to correct a minor clerical error. A copy of the claim amendments can be found in Appendix A. Thus, claims 1-46 are currently pending. A copy of the pending claims is included as Appendix B for the examiner's convenience.

B. **Rejection of Claims 27 and 39 under 35 U.S.C. 112, second paragraph**

Claims 27 and 39 are rejected under 35 U.S.C. 112, second paragraph for lack of antecedent basis in regard to the phrase "the chemotherapeutic agent." Applicants have amended the claims to correct a minor clerical error to read "the chemotherapeutic drug," which has antecedent basis in claim 1. Due to the fact that appropriate correction has been made, Applicants request withdrawal of the rejection.

C. **The Claims Are Not Anticipated by the Cited Reference**

The Action rejects claims 1-46 under 35 U.S.C. §102(e) as being anticipated by Urban *et al.* (U.S. Patent No. 5,814,647) ("Urban"). Applicants respectfully traverse this rejection.

Applicants' invention is directed towards a method for inhibiting the growth of a cancer cell by treating the cancer with a ***combination*** of a thiazolidinedione compound with other therapies, some of which are standard therapies. The combination of such therapies, as set forth in the present application, at least from the bottom of page 15 to the middle of page 17, can result in a non-toxic or lower toxicity treatment, neither of which is taught in the Urban *et al.* reference. In particular, the methods of the presently claimed invention comprise contacting the cancer cell with a thiazolidinedione compound ***and*** a chemotherapeutic drug or irradiating the cancer cell with x-ray irradiation, UV-irradiation, γ-irradiation, or microwaves, in amounts effective to inhibit the growth of the cancer cell. It is not the enablement of Urban *et al.* with respect to use of thiazolidinedione as a cancer therapy that is at issue. Applicants do not raise in any way an issue regarding the enablement of the invention claimed in Urban *et al.* Instead, Applicants challenge the lack of enablement in Urban *et al.* with respect to combination therapy comprising thiazolidinedione and a second anti-cancer therapy that is claimed in the current application. Prior to the Applicants' disclosure, the use of thiazolidinedione in combination with other

chemotherapeutic agents or radiation for the treatment of a cancer cell was not sufficiently ***taught*** in the art to anticipate the claimed invention

For a prior art disclosure to anticipate an applicants' invention, the reference must contain an "enabling disclosure." MPEP §2121.01 (quoting *In re Hoeksema*, 399 F.2d 269, 158 U.S.P.Q. 596 (C.C.P.A. 1968)). Urban does not ***teach*** the use of chemotherapeutic drugs or radiation in combination with a thiazolidinedione. At most, Urban *et al.* suggest that one ***may try*** chemotherapeutic drugs or radiation in combination with a thiazolidinedione. It is well established that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that it is "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement." *Genentech, Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001 (Fed.Cir. 1997). Urban *et al.* fail to enable any method that uses a thiazolidinedione in combination with chemotherapeutic drugs or radiation.

Urban *et al.* merely state, "Use of Troglitazone therapy in conjunction with other chemotherapeutic agents, radiation, or surgery ***may*** in many cases be the preferred mode of treatment." (emphasis added) The mere presence of the words is not sufficient to enable a method of treatment. The absence of an enabling disclosure is highlighted by the fact that unlike the present disclosure, not a single example of a combination therapy is provided in Urban *et al.* This point is made further salient given that the Examiner earlier admitted that the therapeutic effects of a thiazolidinedione compound in combination with other therapy in treating cancerous cells was "**unpredictable**" particularly **"with regard to the state of the art at the effective filing date of this application**." Office Action Dated 8/16/2000 at page 5 (emphasis added), rejecting claim directed to combination therapy (claim 16, for example). If the concept of cancer

therapeutics is considered unpredictable, the lack of any evidence in Urban *et al.* that the claimed combination therapy works demonstrates that that reference is not sufficiently enabling.

Moreover, the Urban *et al* reference is deficient compared to the present application for other reasons as well. Applicants note, for example, that Urban *et al.* does not indicate in any way that a combination therapy would result in a therapy with a *lowered* toxicity. In particular, the present specification shows that a reduction in the dose of 5-FU by a factor of 100 (see specification, at least on page 57 lines 25-28 and FIG. 5) still achieves therapy, which would not have been known or predicted from the disclosure of Urban *et al.* alone or in combination with teachings of the prior art. Thus, one of skill in the art at the time the present application was filed would not have expected that the combination of thiazolidinedione therapy with chemotherapy or radiation therapy would result in an improved method of cancer treatment.

At most, the mention of combination therapy in Urban *et al.* was a mere suggestion, the enablement of which is not sufficiently supported by that reference. Clearly, with regard to the presently claimed invention, the current rejection relies heavily on the teachings of the *present* application to (1) enable the disclosure of Urban *et al.* and (2) provide an expectation of success in light of the art, which the Examiner believed was generally unpredictable.

Furthermore, even if one were to construe the words of Urban *et al.* as enabling, Urban *et al.* speak only to a genus of chemotherapeutic agents. Reference to a genus of chemotherapeutic agents cannot anticipate the species of chemotherapeutic agents as set forth, at least, in claims 17 to 24 of the present invention. These claims are clearly not anticipated by the cited reference.

The Urban *et al.* reference does not contain an enabling disclosure with respect to methods of thiazolidinedione/chemotherapy or radiation combination therapy. Accordingly, for

the above reasons, Applicants contend that the claims are not anticipated and respectfully request that the rejection be withdrawn.

D. The Claims Are Non-obvious over the Cited References

The Action sets forth various obviousness rejections based on the combination of Urban *et al.* with a variety of references. In all of the rejections based on 35 U.S.C. 103 the Urban *et al.* reference is the primary reference. Consequently, all the rejections rely on Urban *et al.* for the teaching of the thiazolidinedione combination therapy. This reliance on the Urban *et al.* reference as ***teaching*** a combination thiazolidinedione therapy is erroneous. As discussed above, Urban *et al.* does not teach any method of treatment that includes contacting the cancer cell with a thiazolidinedione compound ***and*** a chemotherapeutic drug or irradiation in amounts effective to inhibit the growth of the cancer cell.

To establish a *prima facie* case of obviousness the ***teaching***— *i.e.*, instruction, not a mere suggestion—of the claimed combination and the reasonable expectation of success must both be found in the prior art. MPEP §2143 (citing *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991)). A proper *prima facie* case has not been made because these requirements have not been fulfilled. Urban *et al.* does not instruct one of ordinary skill in the art in the methods of combination therapy to inhibit the growth of a cancer cell. The combination of Urban *et al.* with the references cited in the Action does not remedy this defect nor does it render the present invention obvious over the art cited.

Urban *et al.* is said to teach the use of troglitazone therapy in conjunction with other chemotherapeutic agents or radiation; however, a single vague statement is not sufficient to teach a method of treatment using a chemotherapeutic drug or type of radiation in combination with a thiazolidinedione. Urban *et al.* may state a general concept, but this is a far cry, particularly in an area of unpredictability, from teaching or providing instruction in a "method for inhibiting the

growth of a cancer cell comprising contacting the cancer cell with a thiazolidinedione compound and contacting the cancer cell with a chemotherapeutic drug or irradiating the cancer cell with x-ray irradiation, UV-irradiation, γ-irradiation, or microwaves, in amounts effective to inhibit the growth of the cancer cell." Furthermore, there is nothing in the general statement provided by Urban *et al.* that would lead one of ordinary skill in the art to conclude with a reasonable expectation that the combination therapy would be successful. In fact the only true teaching of the method and reasonable expectation of success is found in Applicants' patent application. Accordingly, there is no *prima facie* case of obviousness.

At most, the references disclose that one skilled in the art might find it "obvious-to-try" the claimed invention. An "obvious-to-try" situation exists when a general disclosure piques the scientist's curiosity, "such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued." *In re Eli Lilly & Co.*, 902 F.2d 943, 945, 14 U.S.P.Q.2d 1741, 1743 (Fed. Cir. 1990). The Federal Circuit has consistently held that "obvious to try" is not to be equated with obviousness under 35 U.S.C. §103. *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 725, 16 U.S.P.Q.2d 1923, 1928 (Fed. Cir. 1990).

On this basis alone, the obviousness rejections are inadequate. They are further deficient for the reasons outlined below.

1. Claims 1, 16-25, 28-29 and 36-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Urban *et al.* in view of Medenica *et al.* (U.S. Patent 5,736,129).

Applicants traverse this particular rejection based on the deficiencies of the Urban *et al.* reference, as set forth above, and the lack of a reasonable expectation of success for the

combination therapy provided by Urban *et al.* in view of Medenica *et al.*. The Action relies upon the Medenica *et al.* reference to provide an expectation of success based on the success of prior drug combinations that have no bearing on methods using thiazolidinedione in combination with other chemotherapeutic drugs or irradiation. The basis for such a conclusion can only be the present application itself, which is impermissible. Taking the general suggestion of Urban *et al.* in view of Medenica *et al.* provides no basis for one of ordinary skill to have a reasonable expectation that thiazolidenedione in combination with other chemotherapy agents would be successful, moreover less toxic. The likelihood of antagonism or lack of additivity between components would be just as likely as additive or synergistic effects. Thus, one of ordinary skill in the art would ***not*** have a reasonable expectation that the combination therapy as described in the present application would succeed.

2. Claims 1, 25 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Urban *et al.* in view of Medenica *et al.* (U.S. Patent 5,736,129) and in further view of Jin *et al.* (U.S. Patent 6,251,871).

Applicants traverse this rejection based on the deficiencies of the Urban *et al.* and the Medenica *et al.* reference, as described above, in view of Jin *et al.*. This combination of references also lacks a reasonable expectation of success for the combination therapy. The Action relies upon the Jin *et al.* reference to provide a suggestion for use with thiazolidinedione and an expectation of success based on the success of gene therapies that have no bearing on the present invention. The basis for such a conclusion can only be the present application. The general and vague suggestion of Urban *et al.* in view of Medenica *et al.* and Jin *et al.* provides no basis for one of ordinary skill to have combined the references and to have a reasonable expectation that thiazolidenedione in combination with other chemotherapy agents in addition to gene therapies would be successful. Thus one of ordinary skill in the art would not have

combined the therapies described in the cited references with a reasonable expectation that the combination therapy would succeed.

3. Claims 1, 28, 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Urban *et al.* in view of Roth *et al.* (U.S. Patent 5,747,469).

Applicants traverse this particular rejection based on the deficiencies of the Urban *et al.* reference, as set forth above, and the lack of a suggestion to combine the references with a reasonable expectation of success for the combination therapy provided by Urban *et al.* in view of Roth *et al.*. The Action relies upon the Roth *et al.* reference to provide an expectation of success based on the success of gene therapy agents in combination with DNA damaging agents, the combination of which has no bearing on the expectation of success of methods using thiazolidinedione in combination with other chemotherapeutic drugs, irradiation, and or gene therapies. The analogy between thiazolidinedione and a gene therapy is simply not supported, particularly in light of the deficiencies of the Urban *et al.* reference. The basis for such a conclusion can only be the present application itself. The mere suggestion of Urban *et al.* in view of Roth *et al.* provides no basis for one of ordinary skill to have a reasonable expectation that thiazolidenedione in combination with other chemotherapy agents would be successful. Thus, one of ordinary skill in the art would not have combined the cited references with a reasonable expectation that the combination therapy would succeed.

4. Claims 1, 9, 11-14, 40 and 43-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Urban *et al.* in view of Pitot (In Fundamentals of Oncology, 3rd Edition, pages 29-32).

Applicants traverse this particular rejection based on the deficiencies of the Urban *et al.* reference, as set forth above. The reliance on the Pitot reference to provide for the expansion of the term mesenchymal tumors to include bone cancer cells, precursors of osteosarcoma and osteosarcoma cells does not remedy the deficiency of the Urban *et al.* reference as described